SUMMARY

Infectious disease remains a serious problem in U.S. agriculture in two distinct populations:

• Migrant farm workers experiencing human-host illnesses, often episodic and exacerbated by substandard living and employment conditions.

• All other farm workers experiencing sporadic, isolated illness that is most frequently zoonotic, vector-borne, or environmentally acquired in nature.

Both populations may present risk of exposure to the non-farm population through personal contact, indirect exposure (environment or vector), or contamination of food produce. Obvious innovations and technologies exist to improve disease recognition, management, and control for both groups specifically, and non-farm individuals generally. The broad and varied scope of this problem is presented, including areas that should be targeted for additional research or enhanced program support.□

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AN OVERVIEW OF POTENTIAL HEALTH HAZARDS AMONG FARMERS FROM USE OF PESTICIDES

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Beginning in the mid-1940's, pesticides have become an increasingly important weapon in the attempt to control troublesome agricultural pests. Consequently, agriculture has become a major consumer of pesticides and now accounts for about 65 percent of the total domestic use.[1] Pesticide use varies by the crops and livestock raised, but a majority of farmers report application of some.

In a 1982 survey, approximately 75 percent of the farmers with crops and 70 percent with livestock used pesticides.[2] With 2 million farmers, 6 million additional farm family members, and nearly 3 million hired farm workers, there is a large number of persons with potential contact with pesticides through agricultural use.[3]

Use of pesticides has been an integral component of the agricultural revolution, which over the past 50 years has greatly increased yields. Losses that would occur without the use of pesticides are difficult to estimate, but they could be sizable.[4]

Despite efforts to tailor the toxicologic properties of pesticides to specific pests, the fundamental similarity of all organisms at the subcellular level raises concerns about potential pesticide exposure of a large segment of the population.

Although we should not lose sight of the benefits pesticides provide, the purpose of this review is to evaluate the potential for, and evidence of, adverse health outcomes from pesticide exposure in humans. Acute effects have been well established, and the major focus of this presentation will be on chronic effects.

ACUTE EFFECTS

Effects from acute exposure to pesticides are well established, but statistics on injury and death from acute exposures are incomplete for the United States as a whole. Some results indicate that the number of fatalities fell between the 1950's and the 1970's.[5] Based on extrapolation from a survey of a small number of hospitals, EPA estimated that there were fewer than 3,000 annual admissions to hospitals for pesticide poisoning.[6]

In California, however, where physicians are required by law to report suspected pesticide poisonings to the Department of Food and Agriculture, approximately 2,000 poisonings have been reported annually in recent years.[7] About 50 percent of these were from occupational exposures.

More effective reporting systems are needed before the magnitude of adverse health conditions from acute exposures can be well monitored. Assessments in agriculture should include migrant workers, farm laborers, and dependents of farmers, as well as farm operators.

CHRONIC EFFECTS

Of growing concern are chronic health outcomes that do not occur immediately after exposure, including carcinogenic, developmental, immunological, reproductive, and neurological effects.[8,9] The lengthy interval between exposure and chronic effects makes risk assessment for these outcomes more difficult to evaluate than acute effects.

As testing procedures have improved, concern has increased over long-term health effects from pesticides. Today significant efforts are devoted toward experimental and epidemiologic evaluation of pesticides. The quantity and quality of the data available, however, vary by disease outcome.

Establishment of a formal testing program by the National Cancer Institute (NCI) in 1968 and continued by the National Toxicology Program (NTP) in 1978 gave carcinogenicity screening of chemicals, of which pesticides were an important concern, an early start. This experimental effort stimulated epidemiologic investigation of pesticides and cancer.

The availability of cancer registries also enhanced opportunities for cancer research by providing a readily available source of well-diagnosed cases. Registries for other chronic disease endpoints are only beginning to be established. Since we lack some of these resources, the occurrence of nonmalignant chronic disease from pesticide exposure has not been evaluated as thoroughly.

CARCINOGENIC EFFECTS

Some 47 pesticides have been evaluated in the NCI-NTP bioassay program (Table I).[10] Information from other sources is available, but is not considered here because study protocols sometimes deviate from the preferred model and because the purpose of this paper is to provide an indication of hazards presented by pesticides and not to provide a comprehensive review of all available data.

In the NCI-NTP assays, six pesticides, or 13 percent(chlordecone, dichlorvos, aminotrizole, sulfallate, dibromochloropropane (DBCP), and EDB) were positive in both sexes in mice and rats. Another 10 (21 percent) were positive in both sexes of one species (chlordane, chlorobenzilate, dieldrin, heptachlor, tetrachlorvinphos, toxaphene, nitrofen, captan, chlorthalonil, and dichloropropene). Five (11 percent) were positive in one sex of at least one species (aldrin, dicofol, piperonyl sulphoxide, chloramben, and trifluralin). For 19 (40 percent) there was no evidence of carcinogenicity in any sex/species group and seven (15 percent) provided inadequate or equivocal evidence for carcinogenicity.

Several of the pesticides positive in bioassays are no longer on the market, or their use is severely restricted, but others are widely used. The 16 chemicals positive in both sexes in at least one species include organochlorine and organophosphate insecticides, herbicides, fungicides, and fumigants, suggesting that no chemical class of pesticides can be considered problem free.

Pesticides are selected for testing for various reasons, including suspicion of carcinogenicity. With 45 percent of the pesticides tested showing some evidence of carcinogenicity, the concern about chronic human exposure would seem well founded.

Table I. Results of Carcinogenicity Testing of Pesticides from the National Toxicology Program of Bioassays in Mice and Rats (modified from reference 10).

	MICE		RATS	
	M	F	M	F
INSECTICIDES				
Aldicarb	–	–	–	–
Aldrin	+	–	E	E
Azinphosmethyl	–	–	E	E
Chlordane	+	+	–	–
Chlordecone	+	+	+	+
Chlorobenzilate	+	+	E	E
Coumaphos	–	–	–	–
Diazinon	–	–	–	–
Dichlorvos	+	+	+	+
Dicofol	+	–	–	–
Dieldren	+	+	–	–
Dimethoate	–	–	–	–
Dioxathion	–	–	–	–
Endosulphan	I	–	I	–
Endrin	–	–	–	–
Fenthion	E	–	–	–
Heptachlor	+	+	–	–
Lindane	–	–	–	–
Malathion	–	–	–	–
Maloxon	–	–	–	–
Methoxychlor	–	–	–	–
Methyl parathion	–	–	–	–
Mexacarbate	–	–	–	–
Parathion	–	–	E	E
Phosphamidon	–	–	E	E
Photodieldrin	–	–	–	–
Piperonyl butoxide	–	–	–	–
Piperonyl sulphoxide	+	–	–	–
Tetrachlorvinphos	+	+	–	+
Toxaphene	+	+	E	E

	MICE		RATS	
	M	F	M	F
HERBICIDES				
Aminotriazole	+	+	+	+
Chlorambene	+	–	–	–
Fluometuron	E	–	–	–
Monuron	–	–	+	–
Nitrofen	+	+	E	+
Sulfallate	+	+	+	+
Trifluralin	–	+	–	–
FUNGICIDES				
Anilazine	–	–	–	–
Captan	+	+	–	–
Chlorthalonil	–	–	+	+
Fenaminosulf	–	–	–	–
O-Phenylpheno-l	–	–	–	–
Pentachloro-nitrobenzene	–	–	–	–
Triphenyltin-OH	–	–	–	–
FUMIGANTS				
DBCP	+	+	+	+
Dichloropropene	I	+	+	+
EDB	+	+	+	+

E = Equivocal
I = Inadequate evidence
M = Male
F = Female

Pesticides may exert their carcinogenic effects through several mechanisms, including mutation, inhibition of gap-junctional cellular communication, peroxisome proliferation, and other promotional activities.[11] In an evaluation of genetic damage from 65 pesticides in 14 *in vivo* and *in vitro* tests, the nine chemicals were found to be active in most assays. These included organophosphate insecticides (acephate, demeton, monocrotophos, and trichlorfon), phthalimide fungicides (captan and folpet), and thiocarbamate herbicides (diallate, sulfallate, and triallate).[12]

Another group of 26 chemicals were positive in some tests, but were generally less active than the nine chemicals above. Pesticides in this group included phenoxy herbicides (2,4-D and 2,4-DB); organophosphate insecticides (azinphos-methyl, crotoxyphos, disulfoton, and methyl parathion); ethylenebisdithiocarbamate fungicides (manzeb, maneb, mancozeb, and zineb); and pyrethroid insecticides (allethrin, chrysanthemic acid, and ethyl chysanthemate). Thirty pesticides gave no evidence of genetic toxicity.

Some pesticides may influence the carcinogenic process in an epigenetic manner. For example, inhibition of intercellular communication can disrupt development or promote cancer.[13]

Broad occupational surveys from around the world have noted rather consistent excesses of leukemia, non-Hodgkin's lymphoma, multiple myeloma, soft-tissue sarcoma, and cancers of the brain, skin, lip, stomach, and prostate among farmers.

A number of pesticides have been shown to inhibit gap junction intercellular communication including DDT, dieldrin, chlordane, heptachlor, Kepone, mirex, and endrin.[14] Several of these pesticides have been shown to have a promotional effect on liver carcinogenesis in the rat.[11]

Peroxisome proliferation and the resultant increased generation of hydrogen peroxide represent another possible non-genotoxic carcinogenic mechanism. Phenoxy acid herbicides appear to be peroxisome proliferators in several rodent species.[11] Much of the epidemiologic data available on the carcinogenicity of pesticides comes from studies of persons employed in agriculture.

Broad occupational surveys from around the world have noted rather consistent excesses of leukemia, non-Hodgkin's lymphoma, multiple myeloma, soft-tissue sarcoma, and cancers of the brain, skin, lip, stomach, and prostate among farmers.[15-17] These excesses occur against a background of lower overall mortality, particularly for heart disease and other cancers including lung, colon, bladder, kidney, esophagus, and liver. This pattern of low mortality from most causes of death, but excesses for a few cancers, suggests a role for work-related factors.

The low prevalence of smoking among farmers is probably related to their more favorable rates for heart disease and cancers of the lung, esophagus, and bladder.[15] High levels of physical fitness may contribute to their lower rates of colon cancer and heart disease.[17]

Case-control and other studies provide further evidence that farmers are at higher risk for selected cancers than the general population. In a recent survey of the literature,[17] excesses among farmers were seen in 12 of 13 studies of leukemia, 12 of 15 studies of Hodgkin's disease, 14 of 19 studies of multiple myeloma, 18 of 29 studies of non-Hodgkin's lymphoma, three of three studies of lip cancer, three of three studies of skin cancer, five of seven studies of brain cancer, three of five studies of soft-tissue sarcoma, six of six studies of stomach cancer, and two of three studies of prostate cancer.

The excesses for specific cancers among farmers may have broad public health implications, since several of the high-rate tumors appear to be increasing in the general population of many developed countries.[18] Of special interest are the rising rates for multiple myeloma, non-Hodgkin's lymphoma, melanoma, and cancer of the brain.

In England and Wales[19] and the United States[20], prostate cancer has also been increasing. Changes in diagnosis and reporting may account for some of the increase for these tumors.[20, 21]

The rising rates for non-Hodgkin's lymphoma, multiple myeloma, and leukemia in agricultural areas of the central United States, however, is a further indication of the possible involvement of agricultural exposures. Excesses of cancer of the brain and lymphatic and hematopoietic system have also been observed in rural farm populations in Quebec.[62]

Risks were correlated with pesticide usage and were observed among women, as well as men, raising the possibility of effects from nonoccupational exposure. The specific agricultural factors that might account for the cancers excessive among farmers have not been definitively identified, but a number of etiologic clues exist.

Exposures of interest include pesticides, fertilizers, fuels and engine exhausts, organic and inorganic dusts, solvents, ultraviolet light, and zoonotic viruses.[3] Many, perhaps even most, of the members of the general population may also have contact with some of these substances. Studies of farmers may, therefore, provide explanations for the rising incidence of certain cancers among the general population.

Although farmers come into contact with a variety of potentially hazardous substances, pesticides have received the most attention in epidemiologic studies, possibly because several pesticides are carcinogenic in bioassays.[10] Early epidemiologic investigations evaluated cancer risks associated with pesticide exposure in general.

The International Agency for Research on Cancer (IARC) in a recent deliberation concluded that exposures occurring during the application of insecticides were probably carcinogenic in man.[22] Cohort studies of applicators and manufacturers of insecticides have tended to show excesses of cancers of the lung and the lymphatic and hematopoietic system, although some investigations show deficits.[10, 11]

In these studies it was not possible to determine the specific chemicals accounting for these excesses, but most subjects were employed during a time when organochlorine insecticides were the chemicals used predominately. Although many epidemiologic studies have evaluated cancer risks among farmers and other pesticide-exposed workers,[17] only recently have there been attempts to assess risks from exposure to specific pesticides.[23]

Among those studies that have, soft-tissue sarcoma, Hodgkin's disease, non-Hodgkin's lymphoma, leukemia, and lung cancer have been associated with DDT;[22, 24-28] non-Hodgkin's lymphoma with organophosphates;[25] soft-tissue sarcoma with a variety of animal insecticides[24]; leukemia with crotoxyphos, dichlorvos, famphur, pyrethrins, methoxychlor, and nicotine[26]; and non-Hodgkin's lymphoma[25, 29-33] and soft-tissue sarcoma[34-38] with phenoxyacid herbicides. A potential problem for other cancers is suggested by an important study of workers engaged in the production of 2,4,5-

Table II. Pesticide Effects on the Immune System (modified from reference 39).

Pesticide	Species	Summary of Effects
▸ ORQANOPHOSPHATES		
Methylparathion	Rabbit	Thymus atrophy and reduced DTH response.
	Mouse	Decreased host resistance to infection *Salmonella typimurium*.
Parathion	Mouse	Altered colony forming activities of bone marrow stem cells.
Malathion	Mouse	Suppression of CTL response *in vitro*.
▸ ORQANOCHLORINES		
DDT	Rabbit	Thymus atrophy and reduced DTH response.
Mirex	Chicken	Decreased IgG levels.
Hexachlorobenzene	Mouse	Increased sensitivity to endotoxin and malaria challenge.
	Rat	Increased humoral immune responses to tetanus toxoid and delayed-type hypersensitivity to ovalbumin.
Dieldrin	Mouse	Decreased AFC response and increased susceptibility to viral infection.
Chlordane	Mouse	Decreased contact hypersensitivity after *in utero* exposure.
	Mouse	Suppression of AFC responses and T-cell activity in a MLC reaction following *in vitro* exposure.
▸ CHLOROPHENOXY COMPOUNDS		
Pentachlorophenol	Mouse	Decreased host resistance to virus-induced tumor metastases.
2,4-D	Mouse	Enhanced T- and B-cell responses following dermal application.
▸ CARBAMATES		
Carbofuran	Rabbit	Reduced DTH response.
	Mouse	Decreased host resistance to *Salmonella tvphimurium* infection.
Aldicarb	Mouse	Decreased AFC response to sheep erythrocytes.
	Human	Increased response to Candida antigen, increased number of lymphocytes expressing CD8 markers and decreased CD4+/CD8+ cell ratio.
	Mouse	No alterations in AFC response, B- or T-lymphocyte mitogenesis, host resistance to influenza virus infection, CTL response or percentages of T-cells, T-cell subpopulations or B-cells.

DTH = delayed-type hypersensitivity.
CTL = cytotoxic T lymphocytes.
AFC = antibody-forming cells.
MLC = mixed lymphocyte culture.

trichlorophenol and derivative herbicides, products contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin.[38] In this report, 20 years after first exposure, a significant 50 percent excess of total cancer occurred among workers employed for more than one year while no excess occurred among those employed for less than one year.

Risks were elevated for soft-tissue sarcomas and cancers of the esophagus, stomach, intestines, larynx, lung, and prostate. In the 20-year latency category, lung cancer increased with duration of exposure with standardized mortality ratios (SMRs) of 96, 126, 146, and 156 for duration of exposure categories of < 1 year, 1 to < 5 years, 5 to < 15 years, and 15 or more years, respectively.

IMMUNOLOGIC EFFECTS

Pesticides have immune effects that are of interest in their own right, but they may also be an important mechanism in carcinogenesis. A critical role for suppression of immune responsiveness by pesticides has been demonstrated for infectious disease and maybe for other diseases.[39]

Pesticides have displayed a variety of effects on the immune system (Table II), including suppression of cytotoxic T lymphocyte (CTL) response by malathion, thymus atrophy and delayed-type hypersensitivity (DTH) response by methyl-parathion and DDT, decreased antibody-forming cells (AFC) responses from dieldrin and chlordane, enhanced T-and B-cell responses by 2,4-D, and reduced DTH and host resistance by carbofuran. As with carcinogenicity, immunologic effects are observed from pesticides in various chemical classes (organochlorines, organophosphates, carbamates, and phenoxy-acids). *In vitro* studies of human leukocyte functions have also shown inhibition of blastogenic stimulation[41].

Lymphocyte PHA stimulation was reduced 10 percent by carbamates, 11 to 18 percent by organophosphates, and 11 to 17 percent by organochlorines. Contact dermatitis and allergic chemical dermatitis are well-recognized health effects from pesticide exposure and can occur from exposure to various insecticides, fungicides, and fumigants.[42,42]

Immunologic evaluations of pesticide exposure in humans are in their infancy. Effects observed in animals are not always seen in human studies.[40] For example, altered numbers of T-cells and a decreased ratio of CD4/CD8 T-cells were found in women exposed to aldicarb-contaminated drinking water.[43] In investigations of aldicarb in mice, one noted an inverse dose-related suppression of antibody response,[44] while the another study did not.[45]

> A critical role for suppression of immune responsiveness by pesticides has been demonstrated for infectious disease and maybe for other diseases.

There is also the possibility of a linkage between immunologic effects from pesticide exposure and cancer. It is well documented that patients with naturally occurring or medically induced immunodeficiencies experience striking excesses of non-Hodgkin's lymphoma.[46-50]

In addition, excesses of leukemia and stomach cancer have been observed among persons with primary immunodeficiency syndromes, while increases of soft-tissue sarcoma, melanoma of the skin, and squamous carcinomas of the skin and lip have been observed in renal transplant patients.[49,50] The fact that several of the tumors excessive among farmers (e.g., non-Hodgkin's lymphoma, leukemia, skin, lip, and stomach) also occur among immunodepressed patients could be a coincidence, but it may suggest that effects on the immune system play a role in farming-related cancers.

Epidemiologic investigations of alterations of the immune system are difficult because of large interindividual variability and the confounding effects from infections, drug use and other factors that influence immune responses. Alterations in immune responses may also be short lived.

Monitoring of the immune system over an extended period may be necessary to determine the relevance of any alterations to subsequent disease risk. Consequently, it may be necessary to rely primarily upon experimental investigations in the near future. Thomas, *et al.*,[40] note two important criteria in extrapolating experimental results to humans.

▸ First, the pharmacologic pattern for the pesticide should be the same in humans as in the animal model. This is difficult to achieve because information on absorption, distribution, biotransformation and excretion for the chemical of interest is rarely available in both humans and the animal model.

▸ Second, the human end point of interest must be appropriate for the species selected.

NEUROTOXIC EFFECTS

The nervous system of the pest is the target for many pesticides, so the fact that there are acute neurotoxic effects in humans is not surprising. Anecdotal case reports and epidemiologic studies also suggest that some neurologic symptoms may persist for years.[51]

Chronic effects observed include tremors, anorexia, anemia, muscular weakness, hyperexcitability, EEG pattern changes, insomnia, irritability, convulsions, headache, dizziness, and depression. These occur from various insecticide classes including organochlorines, organophosphates, and carbamates.[51]

Many of the above symptoms developed among workers with prolonged exposure to Kepone (chlordecone) in the Hopewell incident.[52] The symptoms gradually disappeared over an 18-month period, but symptoms persisted after several years in seven of the 23 most severely affected patients.[53]

Less information is available concerning neurotoxic effects from herbicide exposure. Neuromuscular rigidity has been observed in rats after phenoxyacid exposure (2,4-D and MCPA)[54,55] and peripheral nerve conduction velocities were slowed among workers engaged in the manufacture of 2,4-D and 2,4,5-T.[56]

Other nervous system conditions may be associated with pesticide exposure. A case report of Guillain-Barré syndrome noted recent skin exposure to the cotton defoliant, merphos.[57]

An association with spraying of pesticides was reported in a case-control study of idiopathic Parkinson's disease.[58] Risk of Parkinson's disease was also associated with longer duration farming and exposure to pesticides in a study in Hong Kong.[59]

In another case-control study, however, it was associated with a rural residence and drinking well water, but not with use of pesticides.[60] The subjective end points noted in most human studies of neurologic conditions make epidemiologic investigations difficult.

Evaluation of these end points is generally not possible in animals. Closing the gap between the two approaches is critical for a thorough evaluation of neurotoxic effects of chronic pesticide exposure.

REPRODUCTIVE EFFECTS

Mattison *et al.* classify reproductive toxicants as direct-acting or indirect-acting.[61] Direct-acting toxicants may resemble a biologically important molecule and function as agonists or antagonists in the reproductive process.

They may also have direct effects because of their chemical reactivity. Most chemically-reactive substances are cytotoxic, carcinogenic, or mutagenic.

Indirect-acting reproductive toxicants include chemicals that must be metabolized to produce effects, those that interfere with critical enzyme systems, or those that enhance or suppress secretion or clearance of critical control chemicals. Some chemicals may act both directly and indirectly. For example, activities for organochlorine insecticides are suspected to act directly through estrogen receptors and indirectly through prohormone hepatic induction.

Reproductive effects of specific pesticides have recently been reviewed by Mattison *et al.*, 1990.[61] Adverse outcomes in experimental and/or epidemiologic investigations have been reported for DBCP, chlordecone, ethylene dibromide, and carbaryl in males and DDT, chlordecone, lindane, organophosphates, and carbamates among females.

Effects among males have included disruption of spermatogenesis by DBCP, reduced sperm motility and viability by chlordecone, abnormal sperm morphology and sterility by ethylene dibromide, and sperm abnormalities by carbaryl. In animals, studies have noted reduced egg shell thicknesses from DDT, reduced egg production and number of offspring from chlordecone, increased estrone metabolisms by liver microsomal enzymes by lindane, reduced egg production by organophosphates, and reduced fertility by carbamates.

CONCLUSIONS

Experimental and epidemiologic investigations indicate that pesticides can cause a variety of adverse effects including carcinogenicity, immunotoxicity, neurotoxicity, and reproductive toxicity. From this brief review several points stand out.

▸ First, the carcinogenicity of pesticides has been more thoroughly evaluated than other toxic effects and approximately 45 percent of the chemicals tested had an effect in at least one sex of one species in NCI-NTP bioassays. If this experience is relevant to other end points, the potential for any type of adverse outcome from pesticide exposure could be considerable.

▸ Second, the specific pesticides that are positive in the various toxicologic tests do not appear to be restricted to a few chemical classes. Effects are noted from insecticides (organochlorines, organophosphates, carbamates, and pyrethrins), herbicides, and fungicides.

▸ Third, adverse outcomes have been noted in epidemiologic, as well as experimental investigations, indicating that humans are also at risk.

RECOMMENDATIONS

1. Given the evidence for adverse health outcomes from pesticides, enhanced efforts are needed to control exposures in agriculture and elsewhere.

2. More thorough evaluations (experimental and epidemiologic) are needed to more fully characterize the potential adverse effects that may occur from pesticide exposures.

3. Epidemiologic investigations must focus on exposures to specific pesticides. This will require detailed exposure assessment procedures to characterize the type and intensity of exposures.

4. Studies of farm populations should receive a high priority given the widespread use of pesticides in agriculture and the potential for exposure among farmers and farmer laborers, and their dependents.

Retrospective designs can be used to address specific questions, but prospective studies should also be initiated. Prospective investigations provide the opportunity to obtain information on exposure as it occurs, which would eliminate the potential for response bias and would minimize exposure misclassification. Once exposures are well characterized, prospective designs can also be used to evaluate a number of adverse health outcomes, a highly efficient approach in these times of funding limitations.□

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GASES, VAPORS, LIQUIDS, AND DRUGS

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INTRODUCTION

A wide range of gaseous and liquid hazards exists in agriculture (Table I).[1,2] Virtually all of the gaseous hazards from which we can anticipate health effects exist in one form or another in general industry.

While we know of their existence in agriculture, only a few of these hazards have been surveyed in farm settings. We do not know how frequently (on the average) farmers are exposed to individual agents. We do not know the range of concentrations of such exposures. We do not know the extent of the health effects except for the occasional severe case report or fatality.

And if we really did know these parameters, we face yet another challenge; how to translate them into "agricultural hygiene," the industrial hygiene paradigm of "anticipation, recognition, evaluation, and control" learned in general industry over the past 50 years. As we begin to apply this paradigm, another challenge is to understand the limitations of rote transferral of this paradigm from general industry to agriculture without also understanding its nature and its culture.

This presentation will begin with a review of some of these agents, their sources on the farm, and some of the limitations of the traditional hierarchy of controlling these hazards either at their source, along the pathway of the exposure route, or at the receiver (in this case the farmer or farm worker). A discussion of health effects will be minimized except for agents that are by-and-large unique to agriculture.

Table I. Typical Toxic Agricultural Liquids, Gases, and Vapors.

Ammonia	from urine, urea, and anhydrous
Carbon dioxide	animal respiration and combustion
Carbon monoxide	combustion sources
Hydrogen sulfide	manure gas
Nitrogen dioxide	from fresh silage
Oxygen Depletion	asphyxiation in confined spaces
Pesticides	primarily dermal absorption hazards except fumigants
Welding	fumes and gases
Fuel storage	leaks and fires
Fuel and waste oil	skin cancers and dermatitis
Liquified Propane [LP] gas	fires
Liquified anhydrous ammonia	dermal injury

DEFINITIONS

I feel obliged to define a few terms and concepts ingrained into industrial hygiene folklore. The first (Figure 1) is the paradigm of anticipation, recognition, evaluation, and control. Historically, this process began with the recognition of adverse health effects existent within a working population.

- **Anticipation** is the prospective application of dose-response knowledge generated either in the laboratory or in other industries.
- **Recognition** requires the commitment of farmers, interested farm groups, and governmental agencies to survey both the farming environment and the health status of farmers.
- **Evaluation** must develop new ways to interpret surveillance data from the farm setting for the agricultural population.
- **Control** includes not only "hazard communication" but also modified sources and interruptions in the pathways of exposure before the farmer, with or without personal protection, is dosed.

Figure 1. The Agricultural Hygiene Paradigm.

Today, we can anticipate (and hopefully avoid) adverse health effects based on toxicology or prior experiences in other work settings. To evaluate the degree of risk, we have developed a system of "performance based" exposure limits guidelines (guidelines called Threshold Limit Values [TLVs] and their regulatory equivalents called Permissible Exposure Limits [PELs]), the goal of which is to prevent adverse health effects by keeping exposures and doses to acceptable low levels without specifying the method or "work practices" to achieve those levels.

The second is a concept that adverse health effects are the culmination of an often-complex chain of events beginning with the agent emanating into the working environment from a sometimes nebulous source and traveling through a physical pathway to create either an airborne, dermal, or even oral dose; the dose is generally dependant upon the duration of exposure and the degree of personal protection being used by the worker; the agent may act at the site of contact or be absorbed into the body and be transported to some biological target organ where it acts toxicologically to create a clinically identifiable effect.

Over the years, a hierarchy of control options has been inculcated into the profession whereby controlling the source is the preferred option, controlling the pathway between the source and worker is the second option, and controlling the receiver is the third and least preferred option. Hygienists believe that respirators or other forms of personal protective equipment are not a quick cure-all, contrary to popular belief. And even when they are recommended, good practice dictates (and OSHA now requires) that the respirator should be selected based on the measured level of exposure.

GASES AND VAPORS

The following history of silo gas is representative of the fragmented progression of anticipation, recognition, evaluation, and control of a potentially common agricultural health hazard.

Occupational hazards associated with silo gas were first reported in 1914 via case studies of four fatalities of farmers working in and among their freshly filled silos. Their deaths were attributed to carbon dioxide (CO_2).[3]

It was not until the 1950's (30 to 40 years later) that investigations revealed the presence and importance of nitrogen dioxide (NO_2).[4-6] The major portion of toxic NO_2 appears to be produced from organic nitrates, aggravated by the addition of heavy nitrate fertilizer and/or drought conditions.[6]

The process of NO_2 production begins within hours of ensilage, peaks in three to seven days, but may last for up to two weeks. Levels of NO_2 as high as 200 ppm have been reported seven days after filling;[6-7] this is well over its current TLV of 3 ppm (with a 5 ppm STEL).

Our broad understanding of the magnitude and frequency of this hazard is limited by a lack of systematic environmental surveillance and poor reporting of farm injuries and fatalities. Our understanding of its overall impact on the health of farmers is further limited by the difficulty in diagnosing nonfatal cases of the disease due to the multiple and usually latent phases of its clinical manifestations.[8-10] Thus, the severe and fatal cases of silo fillers' disease that are reported probably represent the tip of the proverbial iceberg.

A few systematic surveys have recently been made of chronic gaseous hazards in modern semi-enclosed animal production buildings. Mulhausen[11] found that air quality in poultry barns frequently exceeded exposure limits of 25 ppm for ammonia (NH_3) during fall and winter and sometimes even exceeded its STEL of 35 ppm; H_2S was undetected. Donham

et al.[12,13] surveyed similar swine barns and found 50 percent exceeded the TLC for ammonia; many of these buildings also exceeded the TLC for CO_2, H_2S, and CO (from un-vented space heaters).

Source: urine (urea)-wet floors, slats, gutters, etc.

Anticipated Health Hazards:

Irritating to eyes, nose, trachea (wet body parts)	10-15 ppm
TLV = recommended exposure limit (for gas)	25 ppm
Absorbed into an aerosol may provoke bronchitis, asthma, or other pulmonary effects	<20 ppm

Figure 2. Ammonia (NH_3).

At these concentrations, ammonia by itself would only be a strong irritant to the eyes, nose, and throat. However, in both poultry and swine farm settings, it may be important to consider the simultaneous presence of both ammonia and organic dust aerosols at levels often in excess of 5 mg/m^3. The hypothesis here is that the pulmonary damage caused by ammonia could be considerably greater if the gas were adsorbed onto a respirable-sized aerosol (Figure 2).

In addition to hydrogen sulfide, mercaptans and organic acids (such as methyl and ethyl-mercaptan, carbonyl-sulfide, skatole, and propionic, butyric, and valeric acids) have been identified in the gases emanating from the anaerobic decay of manure typically stored in a pit under most hog and some dairy barns.[14-15] It should be acknowledged that under normal barn conditions, hydrogen sulfide is not at levels of great health concern (Figure 3).[12, 13]

Source: anaerobic manure digestion	
Anticipated Health Hazards:	
Threshold of odor detection	0.1-0.2 ppm
Offensive odor	3-5 ppm
TLV = recommended exposure limit	10 ppm
Olfactory paralysis (cannot be smelled)	25-100 ppm
Serious eye injury (gas eye)	50-100 ppm
Bronchitis (dry cough)	100-150 ppm
Pneumonitis and pulmonary edema	200-500 ppm
Rapid respiratory arrest (death)	>1000 ppm

Figure 3. Hydrogen Sulfide (H_2S).

However, when the manure is agitated prior to pump-out to be returned to the fields as fertilizer, it is rapidly released into the air above the frothing liquid.[15-19] During agitation, the author has measured levels of H_2S as high as 300 ppm at pig breathing height and 1500 ppm in the pit (Figure 4).

• Methyl-mercaptan	• Propionic acid
• Ethyl-mercaptan	• Butyric acid
• Carbonyl-sulfide	• Valeric acid
• Skatole	

Figure 4. Mercaptans and Organic Acids Associated with Hydrogen Sulfide from Manure.

Manure gas deaths often involve multiple victims during futile rescue attempts.[17, 20] As was the case with silo gas, manure gas deaths even as recently as 1989 are sometimes mis-diagnosed as asphyxiation from methane.[20]

Control of agricultural respiratory hazards should rely first on reduction at the source, second on ventilation or some other physical barrier to its movement, and third on personal protection. Control of the source of most of the above agents will require further research before the process of gas generation is sufficiently understood to be reduced or avoided.

High rates of ventilation of farm shops or animal confinement building is often resisted by operators who prefer to conserve heat in cold winter climates, and if too much ventilation were installed without consideration of make-up air requirements, high levels of CO could be drawn back down heater exhaust vents (Figure 5).

Source: improperly adjusted heaters or no make-up air	
Anticipated Health Hazards:	
TLV = recommended exposure limit	50 ppm
Induces spontaneous abortions in swine	100-150 ppm
Asphyxiation dependent upon duration of exposure	(2-3 hours at 500 ppm) <15 mins >2000 ppm

Figure 5. Carbon Monoxide (CO).

As in any other industry, the use of respirators should be considered a temporary and supplemental protection. In agriculture there are no trained persons available to assist in the selection, fit, or maintenance of respirators. Thus, when purchased at all, respirators are selected without knowledge of measured levels of exposure and often without even the benefit of an adequate "work practices" evaluation as shall be discussed below.

Table II. Major Groups of Field-Use Agricultural Pesticides.

	Common Commercial Names
INSECTICIDES	
Organophospates	Counter, Parathion, Guthion, Lorsban, Rabon
Carbamate	Temik, Furidan, Lannate, Sevin
Organochlorines	Dieldrin, Lindane, Chlordane
HERBICIDES	
Phenoxy-aliphatic acids	2,4-D, 2,4,5-T, Trioxone
Bipyridyis	Paraquat, Diquat
Triazines	Atrasine, Blasex, AAtrex
OTHER/MISCELLANEOUS	
Thiocarbamates (fungicides)	Thiram, AAtack, Mabam, Maneb, Zineb
Arsenicals (herbicides)	Paris Green, Cacodylic acid
Acentanilides (herbicides)	Alachlor, Lasso, Ramrod
Dicarboximides (fungicides)	Difolitan, Captan
Dinitrotoluidine (herbicides)	Amex, Prowl, Treflan

LIQUIDS

Pesticides are formulated as solids (such as granules and wettable powders), liquids, and gases and vapors (mostly fumigants). Pesticides can present a hazard to applicators,[21-23] to harvesters re-entering a sprayed field,[24,25] and to rural residents via air, water, and even food contamination.[26-28]

Toxicologically, the major field-use pesticides can be broken down into six major chemical groups shown in Table II. Most of these agricultural chemicals present dermal hazards either from absorption directly through intact skin and/or from dermatitis. Some of these insecticides are also used indoors, especially in greenhouses were exposure is often higher[29].

There are two additional groups of non-field agricultural chemicals: one is fumigants (such as phosphine [usually aluminum phosphide or Phostoxin] or a volatile organic like carbon disulfide or ethylene dichloride) used in produce storage areas, and the other is disinfectants (such as chlorine, quaternary ammonia compounds, organic iodides, and cresol-based compounds) used in indoor animal production facilities.[2] Certain of these chemicals present respiratory hazards particularly when used in combinations; other of these liquid chemicals present a risk of contact or an allergic dermatitis.[30]

While a review of pesticide toxicities is being presented separately, they are presented here because they demonstrate an approach to anticipation, recognition, evaluation, and control quite different from general industry. Some level of anticipation was available from the time of registration, but much of that interest was directed toward consumers rather than users who are exposed at much higher levels.

Given that starting point, it is unfortunate that the recognition of hazards to users has often been a protracted process, in some ways no better than the history of many chemicals used in general industry. However, evaluation of exposure, when it finally started to be conducted, was not site nor user specific but was conducted in response to more recent EPA pesticide registration requirements.

EPA then promulgated what amounts to a "use practices standard" in the form of label instructions, which specify the ways the chemical can be safely and legally used. The implication is that if all users follow these instructions, exposure will be sufficiently low to prevent adverse health effects. This process contrasts sharply with general industry where employers are expected to "assure a workplace free from recognized hazards."

Controls under these circumstances have also differed from general industry. It can be argued that the registration process is itself a form of controlling the source, screening out chemicals deemed too hazardous for agricultural use and restricting certain others to "licensed users."

In that sense, a form of hazard communication was adopted by agriculture a little before general industry. However, the EPA registration and labelling process has yet to address the machinery controlling the pathway of exposure.

When it comes to personal protection, control has for a long time been misdirected at airborne versus the dermal route of exposure; and those respiratory controls which are specified, were established without a decision logic common to general industry for over 30 years[31,32]. I am happy to report that EPA is currently developing a respirator selection decision logic at least consistent with a "use practices standard."

One might ask why a "use practices standard" versus a "performance standard" approach used in agriculture. The one asking the question must not be a farmer.

Even if the administrative and support structure were in place to conduct on-site monitoring at each farm or "place of employment," the activities, working environments, and chemical exposure levels in most agricultural settings vary sufficiently by season, day, and even by hour as to make such measurements moot, which is not to say that measurements and even performance standards have no place in agriculture.

For instance, work in animal production facilities is amenable to the application of traditional TLVs, environmental monitoring, and respirator selection criteria. "Use practice standards" have their own limitations; they must account for many variables, thus often making them overly restrictive conducive to low compliance. It remains a challenge for the future to define the conditions favoring either form of standard or to determine if either is even adequate.

The other category of agricultural chemicals is fertilizers. Anhydrous ammonia is the most heavily used fertilizer in production agriculture. Anhydrous ammonia is hazardous to the skin and especially to the eyes because it is highly hygroscopic, highly caustic, and extremely cold (-28°F under pressure).

Almost any eye contact with this chemical will result in permanent blindness.[33] Inhaling high concentrations of ammonia can result is severe damage to the upper respiratory tract, resulting in bronchiectasis as a possible sequela.[34]

Most of the occupational injuries from anhydrous ammonia occur because of faulty couplings, bleeder valves, shut-off valves, broken hoses, or plugged applicator tips. In addition to an established program of preventive maintenance, a pro-active hazard communication for both commercial and private applicators is essential to establish consistent wearing of eye protec-

Table III. Skin Conditions of Agricultural Workers (adapted from reference 2).

Classification of Skin Condition	Agents (examples)
Irritant contact dermatitis	ammonia fertilizers animal feed additives vegetable crops and bulb plants insecticides, herbicides, and fumigants
Allergic contact dermatitis	herbicides and insecticides antibiotic feed additives plants
Photo-contact dermatitis	creosota feed additive plants containing furocoumarins
Sun-induced dermatoses	sunlight
Infectious dermatoses	cattle, swine, and sheep
Heat-induced dermatoses	moist and hot environments
Arthropod-induced dermatoses	chiggers, bees, and wasps

tion and ensuring the availability of clean water to flush eyes and skin in case of contact.

In addition to their fire hazard and intrinsic toxicity, many of the liquids involved in agriculture can produce dermatitis (Table III). Compared to other occupational groups, farmers have a proportionately higher prevalence of skin diseases.[35, 36]

Irritant contact dermatitis is perhaps the most common type of agricultural dermatoses.[35-39] Irritant substances are ubiquitous and include ammonia fertilizers, several pesticides, soaps, petroleum products, and solvents. Avoidance schemes must include work practices to eliminate or reduce exposure to the most irritative substances and/or the use of personal protection equipment.

Allergic contact dermatitis is typified by poison ivy or poison oak reactions. These are exquisite sensitizers as are certain herbicides and pesticides.[2] These reactions are more difficult to control, because susceptible farmers are exquisitely sensitive to very small amounts of offending liquids.

VETERINARY DRUGS

Veterinary drugs are broadly divided into two classes of biologicals and antibiotics (Table IV). Biologicals are made from living products to enhance the immunity of an animal to a specific infectious disease or diseases.

Users of biologicals are at risk of either accidental inoculation or splashing the product into the eyes, mucous membrane, or broken skin. Users at risk include not only veterinarians and their assistants, but also farmers, ranchers, and their employees, except for certain diseases for which a government-regulated control program is in effect (e.g., brucellosis, rabies, pseudorabies).[2]

The most frequent reports of occupational illnesses associated with biologicals involve veterinarians, whether splashing brucellosis strain 19 in their eyes or accidental inoculating themselves. Symptoms may include infection, inflammation, severe localized swelling and pain, and/or an allergic reaction. The infection mimics the acute infection seen from acquisition of the disease directly from either cattle or swine. Disability may last for days to weeks in the worst cases.[40]

Table IV. Veterinary Drugs Potentially Hazardous to Users.

Biologicals	
	Brucellosis strain 19
	Newcastle disease vaccine
	Contagious exthyma (orf) vaccine
	Jhone's disease bacterin
	Escherichia coli bacterins
	Erysipelas vaccines
Antibiotics	
	Penicillin
	Tetracycline
	Sulfamethazine
	Erythromycin
	Virginiamycin

Other products that have been associated with occupational illnesses include Newcastle disease vaccine, contagious ecthyma vaccine, Jhone's disease bacterin, *Escherichia coli* bacterins, and erysipelas vaccines. Newcastle disease and contagious ecthyma (orf) vaccines are live products used in chickens and sheep, respectively.

Workers may contaminate their eyes with Newcastle vaccine as it is being applied inside poultry buildings via a nebulizer, resulting in a moderate conjunctivitis with influenza-like systemic symptoms. Orf vaccine can cause the same pox-like lesions at the site of inoculation as a naturally acquired infection.

Both of these diseases are self-limited and disability will only last for a few days, unless the orf lesions are numerous.[41,42] Injuries induced by the bacterins for Jhone's and *E. Coli*, and by most erysipelas vaccines are limited to the inflammatory response induced by the adjuvants.

Control of these hazards again resides largely in "use practice standards," good animal handling techniques and facilities to prevent the uncontrolled and untimely movements of stressed animals.[43] The use of pneumatic syringes, lock-on needle hubs, and multiple dose syringes will also help reduce injuries.

Eye protection is indicated in many instances. A full-face respirator is recommended while aerosolizing vaccines such as Newcastle, but the other components of a full respirator program are rarely instituted.

Antibiotics are products derived or synthesized from living organisms, mainly mold species of the genus *streptomyces*. Antibiotics are used to treat infectious diseases therapeutically or to improve the rate of gain and feed efficiency in cattle, swine, and poultry.

Again not only veterinarians but also livestock producers and feed manufactures and formulators are exposed to these agents via aerosols of antibiotic-containing feeds within livestock buildings or via aerosols or direct contact while preparing feeds either on the farm or in feed manufacturing plants. The two main occupational hazards are allergic reactions and the development of antibiotic-resistant infections.

The main products used as feed additives include penicillin, tetracycline, sulfamethazine, erythromycin, and virginiamycin. These same products plus many more are used therapeutically. Penicillin is the primary agent that may induce an allergic reaction manifest in the form of a skin reaction from direct contact, or